



ROLE OF PHYTOESTROGENS TO MITIGATE POSTMENOPAUSAL PROBLEMS: A REVIEW

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Abstract

To review the evidence that are available for the mitigation of postmenopausal problems with the phytoestrogens. PubMed, Medline, google scholar and Cochrane electronic database were searched related to role of phytoestrogens in combating the postmenopausal problems in women. Various researches were included related to the postmenopausal symptoms and risk factors like osteoporosis, osteopenia, cardiovascular diseases and cancer. Phytoestrogens act as prudent dietary alternative to Hormone Replacement Therapy (HRT). Soy isoflavones play an important role in the treatment of postmenopausal symptoms as well as in reducing plasma cholesterol levels and cancer prevention particularly breast cancer. Ipriflavone, a synthetic isoflavone responsible to increase in Bone mineral density. Diet rich in phytoestrogens play a beneficial role to mitigate the postmenopausal symptoms and its risk factors.

Key words: Phytoestrogens, Postmenopausal, Mitigation and Isoflavones.

Introduction

Menopause is noteworthy events in woman's life which brings various physiological and psychological changes that affect the quality of her life (Punia, 2017). Menopause is the time when menstrual periods stop permanently causing cessation of pregnancy. In menopause, levels of estrogen and progesterone hormones decrease. Very low estrogen levels after menopause can affect women's health and cause various symptoms including hot flushes in the chest and face, vaginal dryness, night sweats, headache, anxiety, depression, sleep disturbances and other symptoms which may lead to osteoporosis, hypertension, obesity, cardiovascular disease and cancer (Singh, 2014).

According to WHO, "post-menopausal women are those who have stopped menstrual bleeding one year ago or stopped having periods as a result of medical or surgical intervention (Hysterectomy/Oophorectomy) or both" (WHO, 1990). With the increased life expectancy, there is need for considerable improvement in attention to the menopausal health problems in growing population of post-reproductive women (Dalal, 2015). In 2026, projected figures have estimated menopausal population as 103 million among 1.4 billion population (Unni, 2008).

Hormone replacement therapy (HRT) is also suggested to avert post reproductive symptoms (Bairy, 2009). Now-a-days HRT is becoming more challenging because it has side effects as well. Through the diet rich in phytoestrogens, plant-based compound consisting isoflavones, coumestans and lignans plays a protective role to decrease the postmenopausal symptoms. Though various studies have been conducted to assess the post-menopausal symptoms, however literature is limited on the phytoestrogen rich diet to mitigate the post-menopausal problems.

Material and Methods

The PubMed, Medline, Cochrane and google scholar databases were searched for articles using the terms phytoestrogens, postmenopausal symptoms, osteoporosis in postmenopausal women, CVD and Cancer in Postmenopausal women and benefits of phytoestrogens. Published articles included for this review were based on the relevance of research on role of phytoestrogen to mitigate the postmenopausal problems.

Results and Discussion

Phytoestrogens

Phytoestrogens are estrogenic compounds found in plant and encompasses isoflavones, lignans and coumestans. Phytoestrogens are currently the most popular alternative to HRT. Researches have shown that isoflavones have a protective role as compared to lignans and coumestans against the development of various chronic diseases like osteoporosis, cardiovascular disease, and cancers (Duncan, 2003). There are two types of isoflavones *i.e.*, daidzein and genistein. They are found in soy, clover, lentils, beans and chickpeas. A number of studies showed that plant-based diet rich in phytoestrogens is a contributing factor for the decreasing menopausal symptoms, cancer, osteoporosis and heart disease among Asian women.

Postmenopausal Symptoms

During post-menopausal stage, many symptoms occur like hot flushes, night sweats, irritability, sleep disturbance, muscle and joint pain, dry vagina, difficulty in concentrating, depression, mental confusion and headache (Dalal, 2015). A study by Syamala, 2007, observed that the mean age of menopause was 46.24 years. The most common menopausal problems were sleep disturbance *i.e.*, 62.7%, 59.1% muscle

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and joint pain, then 46.4% and 45.6% hot flushes and night sweats respectively. Further, 32.1% postmenopausal women suffered from depression and 21% from anxiety. Another research conducted in Jamnagar district of Gujrat aimed at understanding various post-menopausal symptoms among women aged between 40 and 65 years. The symptoms were higher in urban areas followed by urban slums and rural areas. The common symptoms found were joint pain (64%), backache (58%), irritability (56.66%), forgetfulness and sadness (48%) and vasomotor symptoms like hot flushes and night sweats (47.33%) (Sarkar, 2014).

Phytoestrogen supplements are used as alternative to Hormonal Replacement Therapy (HRT) for the management of postmenopausal symptoms. Vasomotor symptoms like hot flushes, sleep disturbance and night sweats, these are consequences of estrogen deficiency may less observed in Asian women as compared to European or American women because they consuming phytoestrogen rich diet (Freeman *et al.*, 2007; Messina *et al.*, 2006). A study (Aso, 2012) was done on Japanese women, found that 10mg of equol supplement showed beneficial role on menopausal symptoms majorly hot flushes and shoulder or neck stiffness. Another study was done by the randomized double-blind controlled method in which 100mg of soy isoflavones extract was given and it showed significant reduction in hot flushes. So, it can be considered as safe and effective therapy for postmenopausal women (Nahas, 2007). Combination of isoflavones, cumicifuga racemose and lignans also showed an acute positive effect on reduction of postmenopausal symptoms (Sammaritino, 2006). Isoflavones from red clover (promensil) also responsible for the reduction in hot flushes of postmenopausal women (Van de weijer, 2002). Therefore, combination of phytoestrogens supplements with the exercise found as better strategy for reduction of postmenopausal symptoms and improving the postmenopausal quality of life (Riesco, 2011).

Risk factors and complications in postmenopausal women

The Study conducted by Bangalore's institute for social and economic change found there was higher risk of being affected by obesity, osteoporosis, diabetes mellitus, hypertension, dyslipidaemia, cardiovascular disease, and various cancers at the age between 45 to 50 years (Syamala, 2007).

Osteopenia and osteoporosis: In Indian women, osteopenia and osteoporosis are prominent in post-menopausal period. With 35-40% of post-menopausal women to be diagnosed with osteopenia while 8-30% suffer from osteoporosis between 40 and 65 years of age due to diet deficiency (Unni, 2010). This can be reduced by supplementation and dietary changes mainly for calcium (1000-1500 mg daily) and Vitamin D (400-800 IU daily) (Dalal, 2015). As per Cauley (2001), found that Hormone replacement therapy (HRT) is effective in preventing and reducing osteoporosis related fractures by approximately 50% in postmenopausal women.

The reduction in bone mineral density can be prevented through the intake of natural plant-based compound *i.e.*, phytoestrogens or estrogen like compounds in plants. Osteopenia may lead to another severe condition,

osteoporosis that can be characterized by the low bone density and it cause due to deficiency of ovarian hormones (Al-Anazi, 2011). In post-menopausal women, soy isoflavones which having similar structure and functions as 17 Beta-estradiol, an alternative of hormone replacement therapy. These act on the osteoclast and osteoblast both through the genomic and non-genomic pathways and performing many beneficial effects in the reduction of bone density, turnover markers and mechanical strength of bones (Atmaca A, 2008).

Phytoestrogen containing isoflavone has been considered as effective in increasing the bone mineral density in postmenopausal women (Table 2). Ipriflavones may also responsible for the formation of osteoblast and inhibiting the osteoclast activity and it has been measured by the urinary resorption marker detection and biochemical markers of bone resorption and bone mineral density (Valente, 1994).

Cardiovascular Disease: In India, there is rapid increase of CVD in postmenopausal women. Projection of around 42% of deaths by CVD only due to prevalence of metabolic syndrome which includes insulin resistance, altered glucose tolerance or diabetes, dyslipidaemia, hypertension, and central obesity (Unni, 2010). A study was done at Manmohan Memorial Institute of Health Sciences (MMIHS) which analysed Total Cholesterol (TC), Triacylglycerol (TG), High Density Lipoprotein Cholesterol (HDL-C), and Low Density Lipoprotein Cholesterol (LDL-C) and found that lipid levels were highly significantly increased in postmenopausal women when compared to premenopausal women and hence they are more prone to CVD diseases (Pardhe, 2017).

Phytoestrogens mainly isoflavones plays a beneficial role on the cardiovascular system in reduction of LDL (bad cholesterol), increase in HDL (good cholesterol) through which it may protect from cardiovascular diseases (Clarkson TB, 2001). It has been found that 75 mg/day of soy isoflavones may cause reduction in menopausal symptoms in postmenopausal women for 1-2 years also promote beneficial role in reducing LDL cholesterol and triglycerides levels with increase in HDL cholesterol as seen in Table 3. A study revealed that 56mg and 90mg of isoflavones effects the lipid profile as they increase level of HDL cholesterol in postmenopausal women and also reported that messenger RNA level is increased in isoflavone treatment group. Although, the process of soy isoflavones to modify the lipid profile is remain unclear (Baum, 1998). As per another study soy isoflavones have antioxidant property which helps in reducing the risk of atherosclerosis and CVD. It was examined by the markers of lipid peroxidation and LDL resistance to oxidation. Atheroma is formed by the LDL oxidation and which is required for the uptake of LDL macrophage in the artery wall (Wiseman, 2000).

Cancer: Among postmenopausal women, most common type of cancer is breast cancer. A study showed that the risk of breast cancer increased by the presence of both hormone estrogen and progesterone in the postmenopausal women (Chlebowski, 2003). The phytoestrogens *i.e.*, isoflavonoids and lignans plays an important inhibitory role in the initiation and progressive phase of the development of cancer (Adlercreutz *et al.*, 1997). Many epidemiological researches suggested that diet rich in phytoestrogen plays a protective

role in early life before puberty or during adolescence as well as in adult women to fight with the breast cancer as seen in Table 4. Further, epidemiological studies suggest that soy containing diet in adult women is protective with regard to breast cancer and it may be beneficial if consumed in early life before puberty or during adolescence (Krishna, 2004). Murkies *et al.*, 2000 demonstrate that phytoestrogen (daidzein) has the protective role on the risk of breast cancer in postmenopausal women. In the postmenopausal phase, the estrogen and progesterone hormone level decreases but the chances of breast cancer increase with age (Simpson *et al.*, 2005).

Conclusion

Present review article would help in creating awareness about the role of phytoestrogen to reduce the postmenopausal problems like various menopausal symptoms, osteoporosis, cancer and cardiovascular disease, so that they can improve their quality of life. Study may also help to ensure easy transition of women to old age because scarce attention is paid to post-menopausal aged women unless the condition becomes worse. Results may also help to analyze the impact of diet rich in phytoestrogens on physiological problems during post-menopausal age as well as to reduce the future complications.

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Table 1: Phytoestrogens and Postmenopausal symptoms

Author	Study Design	Interventions or Diet	Findings
Aso T <i>et al.</i> , 2012	Double blind placebo-controlled trial	10mg of natural equol	Effective in reduction of menopausal symptoms mainly hot flushes & shoulder or neck stiffness in postmenopausal women
Cancellieri <i>et al.</i> , 2007	Double blind placebo-controlled clinical trial	BIO, herbal supplement with 72mg/dose of isoflavones	Beneficial effect on postmenopausal symptoms and elements of lipid profile
Del Giorno <i>et al.</i> , 2010	Randomized double blind placebo-controlled study, 12 months	40mg of trifoliumpratense	No improvement in menopausal symptoms & sexual satisfaction in postmenopausal
Ferrari <i>et al.</i> , 2009	Randomized double blind placebo-controlled multicenter trial	80mg of isoflavones or 60mg of genestein	Mainly genestein show positive effect on management of hot flushes in postmenopausal women
Nehas <i>et al.</i> , 2007	Randomized double blind placebo-controlled study	100mg/day of soy isoflavone extract	Favorable effect on vasomotor symptoms mainly hot flushes
Penotti <i>et al.</i> , 2003	Randomized double blind placebo-controlled study	72mg of soy derived isoflavones	No significant effect on hot flushes and endometrial thickness
Riesco <i>et al.</i> , 2011	Randomized double blind placebo-controlled study, 6 months	Four estrogen capsules containing 17.5mg of isoflavones	Combination of exercise and phytoestrogen supplementation beneficial to improve the postmenopausal symptoms
Van de weijer <i>et al.</i> , 2002	Randomized double blind placebo-controlled trial	80mg/day of isoflavones from red clover (promensil)	Significant reduction in hot flushes
Sammartino A <i>et al.</i> , 2006	Randomized double blind placebo-controlled trial	Combination of isoflavones, lignans, cimicifuga racemose	Better reduction of postmenopausal symptoms over 24-hour period

Table 2: Phytoestrogens and Osteopenia/ Osteoporosis in Postmenopausal Women

Author	Study Design	Interventions	Results/Findings
Kaardinaal <i>et al.</i> , 1998	Secondary analysis	The isoflavonoids genistein, daidzein and equol and the lignan enterolactone	No difference
Clifton Bligh <i>et al.</i> , 2001	Randomized double blind placebo-controlled trial, 6 months	Rimostil, red clover isoflavone containing daidzein, genistein, formononetin and biochanin	BMD at proximal radius and ulna increased. BMD at proximal radius and ulna increased
Potter SM <i>et al.</i> , 1998	Double bind trial, parallel group	Soy protein containing concentrated isoflavones	Protective role on Bone maintenance
Guthrie IR <i>et al.</i> , 2000	Population based cohort study	Isoflavones rich food, soy bean, milk, grits, tofu, soy and linseed breads	Bone mass density increases in femoral neck
Dalais FS <i>et al.</i> , 1998	Double bind randomized over study	Soy and linseed diet	Increase in bone mineral content, but no changes in bone mineral density
Alexanderson <i>et al.</i> , 2001	Randomized double blind placebo-controlled trial, 3 years	Ipriflavone	No difference in Bone mineral density

Table 3: Phytoestrogens and Cardiovascular disease in Postmenopausal Women

Author	Study Design	Interventions	Results/Findings
Trimareo V <i>et al.</i> , 2016	Cross over trial	Nutraceuticals containing soy isoflavones, dry extract of Angelica sinesis, Morus alba leaf and magnesium	Found effective to reduce menopausal symptoms and improved Cardio vascular risk profile
Washburn <i>et al.</i> , 1999	Randomized double cross over study, 6 weeks	34mg of phytoestrogen	Supplementation of phytoestrogen may reduce Total cholesterol and LDL levels
Wangen <i>et al.</i> , 2001	Randomized double cross over trial, 93 days	Isoflavones	Reduction in LDL and ration of LDL/HDL levels

Teede <i>et al.</i> , 2001	Randomized double blind placebo- controlled trial, 3 months	Soy supplements containing 118mg of isoflavones	Significant decreased in TG and LDL/HDL ratio
Howes <i>et al.</i> , 2000	Randomized double blind placebo- controlled trial, 10 weeks	Isoflavones extract containing biochanin , formononetin, genistein and daidzein	No effect on TC, TG, LDL and HDL
Hodgson <i>et al.</i> , 1998	Randomized double blind placebo- controlled trial, 8 weeks	Isoflavone tablet	No change

Table 4: Phytoestrogens and Cancer in Postmenopausal Women

Author	Study Design	Interventions	Results/Findings
Den Tokelaar <i>et al.</i> , 2001	Cohort Design	urinary genistein and enterolactone	Not finding any protective effects of genistein and enterolactone on breast cancer risk in our postmenopausal
Alison M <i>et al.</i> , 2000	Randomized cross over	Soy protein powder containing genistein, daidzein and glycitein	Inconsistent results seen
Mc Michael phillips <i>et al.</i> , 1998	Randomized placebo-controlled trial	45mg/ day of isoflavones	Short term soy supplements in diet stimulates breast cancer proliferation
Ingram <i>et al.</i> , 1997	Case control	Phytoestrogens	Phytoestrogen rich diet may protect from breast cancer
Zheng <i>et al.</i> , 1999	Case control	Isoflavones	High intake of phytoestrogens rich in isoflavones plays a protective role in breast cancer